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Electric stimulation of the tuberomamillary nucleus affects epileptic activity and sleep—wake cycle in a genetic absence epilepsy model

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Summary Deep brain stimulation (DBS) is a promising approach for epilepsy treatment, but the optimal targets and parameters of stimulation are yet to be investigated. Tuberomamillary nucleus (TMN) is involved in EEG desynchronization—one of the proposed mechanisms for DBS action. We studied whether TMN stimulation could interfere with epileptic spike-wave discharges (SWDs) in WAG/Rij rats with inherited absence epilepsy and whether such stimulation would affect sleep—wake cycle.

EEG and video registration were used to determine SWD occurrence and stages of sleep and wake during three-hours recording sessions. Stimulation (100 Hz) was applied in two modes: closed-loop (with previously determined interruption threshold intensity) or open-loop mode (with 50% or 70% threshold intensity).

Closed-loop stimulation successfully interrupted SWDs but elevated their number by 148 ± 54% compared to baseline. It was accompanied by increase in number of episodes but not total duration of both active and passive wakefulness. Open-loop stimulation with amplitude 50% threshold did not change measured parameters, though 70% threshold stimulation reduced SWDs number by 40 ± 9%, significantly raised the amount of active wakefulness and decreased the amount of both slow-wave and rapid eye movement sleep.

These results suggest that the TMN is unfavorable as a target for DBS as its stimulation may cause alterations in sleep—wake cycle. A careful choosing of parameters and control of sleep—wake activity is necessary when applying DBS in epilepsy.

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Introduction

Electrical deep brain stimulation (DBS) is a promising approach for epilepsy treatment in patients which do not benefit from antiepileptic drugs (Ben-Menachem and Krauss, 2014; Fisher et al., 2010; Morrell, 2006). However, to achieve maximal therapeutic action and prevent side effects it is of high importance to reveal optimal parameters and targets for stimulation. Two modes of stimulation are currently in use. During open-loop (scheduled, continuous) mode stimuli are delivered continuously, irrespective of seizure occurrence. In the case of closed-loop (responsive) stimulation a short train of pulses is delivered only at the seizure onset, which is detected automatically. The latter mode of DBS has some advantages, notably lower risk of adverse effects (because of lesser stimulation duration) and lower power consumption (which is important for implanted stimulators), but it requires an appropriate seizure-detecting algorithm. In spite of obvious beneficial effect of DBS confirmed by recent large controlled clinical studies (Fisher et al., 2010; Morrell, 2011), a lot of questions concerning the application of this method need to be investigated, such as choosing stimulation parameters, modes and brain targets for each type of seizures.

Tuberomamillary nucleus (TMN) is the only source of histamine in the brain and it sends projections to almost all brain regions (Watanabe et al., 1984; Panula et al., 1989, 1990). Being a part of the system regulating sleep—wake cycle, TMN interacts reciprocally with both sleep-promoting preoptic hypothalamic nuclei and wake-promoting system of the basal forebrain and brainstem (Lin et al., 1994, 1996; Rosenwasser, 2009). Single-cell recordings showed that TMN contain several subpopulations of neurons. Wake-related neurons fire with maximal rate during wakefulness and decrease their activity during both slow wave sleep and rapid eye movement (REM) sleep. Another subpopulation of TMN neurons decrease their discharge in slow wave sleep but increase their activity to waking firing rates or even higher during REM sleep (Steininger et al., 1999). Intracerebral histamine injections promote wakefulness and decrease sleep duration while administration of *H*1-antagonists has an opposite effect (Monti et al., 1986; Lin et al., 1988; Ramesh et al., 2004). Similarly, electrical high-frequency stimulation of TMN causing elevation in brain histamine also promotes arousal and EEG desynchronization (Nishida et al., 2007). This data indicates that TMN takes part in the induction and/or maintenance of the wakeful state and REM sleep, i.e. the states that are characterized by desynchronized brain activity.

EEG desynchronization is proposed to be one of the therapeutic mechanisms of DBS in epilepsy (Kerrigan et al., 2004; Nishida et al., 2007). Epileptic seizures represent pathological hypersynchronous activity of large neuronal populations and DBS of certain brain structures could interfere with this activity leading to seizure suppression. Nishida et al. (2007) have compared the effect of high frequency stimulation of two regions, responsible for EEG desynchronization (TMN and perifornical area), on acute seizures induced by chemoconvulsant pentylenetetrazole. They found that, though stimulation of both structures exerted antiepileptic effect, DBS of the TMN was more effective and produced no behavioral alterations. They concluded that the TMN is a potentially promising target for DBS in epilepsy. However, another group of researchers showed seizure exacerbating effect of TMN stimulation in chronic kindling model of epilepsy (Wu et al., 2008). These controversial results do not allow making a clear conclusion on the use of the TMN as a potential target for DBS. Furthermore there are no studies of TMN DBS in genetic models of epilepsy with spontaneous seizures.

In the present study we investigated whether stimulation of the TMN could disrupt epileptic discharges in rats of WAG/Rij strain with genetically determined absence epilepsy (van Luijtelaar and Coenen, 1993; Meeren et al., 2002; van Luijtelaar and Sitnikova, 2006). Absence seizures in these rats represent spontaneously occurring spike-wave discharges (SWDs) with the frequency 7—11 Hz. SWDs are accompanied by behavioral arrest, twitching of vibrissae and facial myoclonic jerks. The probability of SWD occurrence is dependent on the state of vigilance being maximal during light slow wave sleep and passive wakefulness (Drinkenburg et al., 1991). Importantly, SWDs in WAG/Rij rats occur spontaneously, e.g. without any external manipulations, resembling epilepsy in humans. Together with relatively high amount of SWDs (several hundreds per 24 h) this advantage makes WAG/Rij rats a useful model for DBS research.

We proposed that high-frequency TMN stimulation would interrupt SWDs when applying in a closed-loop mode and compared the long-term effect of closed- and open-loop modes on epileptic activity. Further, regarding wake-promoting role of TMN, it was questioned whether electrical stimulation of this nucleus would lead to a disturbance of sleep—wake cycle of the rats.

Methods and materials

Animals

Experiments were performed on male WAG/Rij rats (m = 250—300 g, age 6—12 months). Animals (n = 5) were kept in individual plastic boxes under natural light cycle, with food and water ad libitum. The experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and our protocol was approved by the Institutional Animal Care Committee. All efforts were made to minimize animal suffering.

Surgery

Rats were anesthetized with chloral hydrate (380 mg/kg, ip) and fixed in a stereotactic frame. One monopolar recording electrode was implanted to the frontal cortex of right hemisphere (coordinates AP 2, ML 2, DV 3) and two twisted bipolar stimulation electrodes were implanted bilaterally to the TMN (AP-4,2, ML 1,3, DV 9,8) (Paxinos and Watson, 1998). Reference and ground electrodes were placed above the cerebellum. Stimulation and EEG electrodes were fixed to the skull bone with dental acrylic cement. Rats were allowed 2 weeks for recovery after the surgery.

EEG recording and stimulation

Electrodes were connected to a cable and then to the amplifier (DL304, NeuroBioLab, Ltd.) through a sliding contact. EEG was amplified and filtered (0.1—70 Hz, notch filter ON), digitized (ADC E14-440, L-Card) and recorded using PowerGraph® software.

Stimulation was performed with a constant current physiological stimulator under the following conditions: monophasic square pulses, frequency 100 Hz, pulse duration 300 μs. Two modes of stimulation were used in the study. In the case of closed-loop stimulation the animal received a 1 s train of pulses at the beginning of each SWD (not later than 2 s after the start of the SWD). SWDs were detected by visual inspection of EEG and stimulation was turned on manually. During open-loop mode the rats received stimulation continuously, irrespective of SWD occurrence. To determine the stimulation threshold animals were stimulated in a closed-loop mode with stimulus intensity starting from 30 μA and increasing in steps of 10 μA until three consecutive SWDs were interrupted by stimulation.

Video registration was performed simultaneously with EEG recording.

Experiment protocol

Six recording sessions were performed in each rat, the duration of each session was 3 h: (1) baseline session and threshold determination; (2) closed-loop stimulation (CL); (3) baseline session; (4) open-loop stimulation with amplitude 50% of threshold (OL50); (5) baseline session; (6) open-loop stimulation with amplitude 70% of threshold (OL70). Stimulation sessions were performed on the next day after baseline ones. A 1—2 days interval was added between each stimulation session and the following baseline recording.

As SWD occurrence has circadian rhythmicity (van Luijtelaar and Coenen, 1988), all recording sessions were performed at the same time of day.

EEG was visually analyzed and the number and duration of SWDs during baseline and stimulation sessions were measured.

Sleep—wake cycle analysis

Based on visual assessment of EEG and video recordings, four wake-sleep stages were distinguished active wakefulness (AW), passive wakefulness (PW), slow wave sleep (SS) and rapid eye movement sleep (REM). For each stage total and mean duration as well as number of episodes were determined and compared between baseline and stimulation sessions.

Histology

After the end of experiments rats were anesthetized with chloral hydrate (400 mg/kg) and perfused with saline followed by 4% formaldehyde. Their brains were removed, stored overnight in 4% formaldehyde and then in 30% sucrose. The brains were sliced in 80 μm coronal sections, stained with cresyl violet and visually assessed under microscope to verify the position of electrode tips. Only animals with stimulation electrodes in the TMN were included in this study.

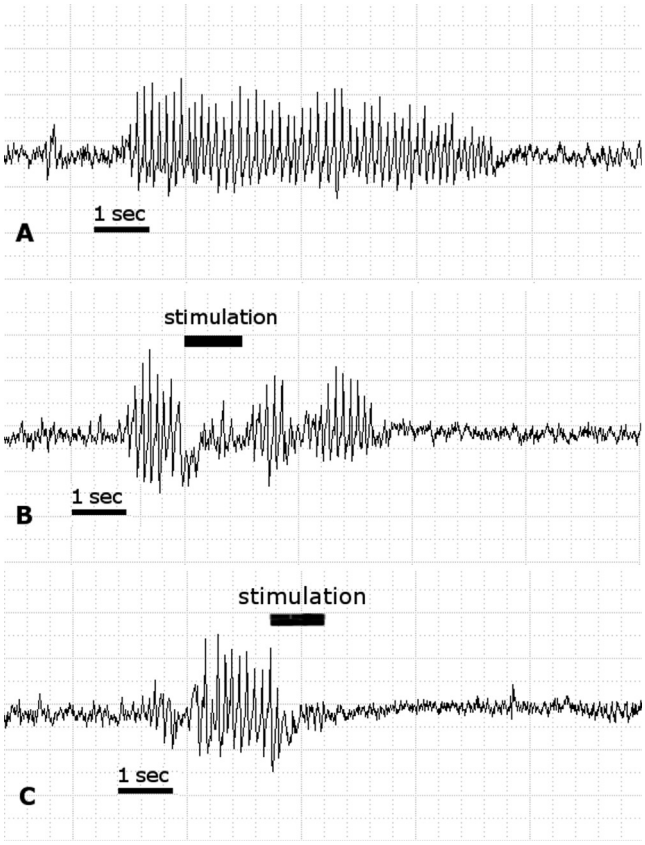

Fig. 1 The effect of closed-loop TMN stimulation on SWDs. (A) SWD in baseline, no stimulation; (B) subthreshold stimulation; (C) threshold stimulation, successive interruption of the SWD.

Statistics

All data are represented as mean ± S.E.M. Friedman ANOVA followed by post-hoc Newman—Keuls test was used for comparisons. Differences were considered statistically significant at the 95% level ($p < 0.05$).

Results

High-frequency closed loop TMN stimulation interrupts ongoing SWDs but increases their occurrence

During the threshold determination session the ability of TMN stimulation to stop ongoing epileptic activity was tested. We found that short-term high frequency stimulation of the TMN applied at the beginning of SWD (closed-loop mode) was able to cause its interruption (Fig. 1) with the mean threshold amplitude being 78 ± 10 μA. Threshold stimulation was usually (but not always) accompanied by a short movement (head nodding, head turning, a small

Table 1 Changes in the total duration of different sleep—wake stages during TMN stimulation in a closed-loop and open-loop modes ($n = 5$).

	Baseline (s)	CL	OL50	OL70
AW	2455 ± 442	—	—	↑* 198 ± 100%
PW	4075 ± 358	—	—	—
REM	361 ± 142	—	—	—
SS	3912 ± 442	—	—	↓* 56 ± 19%

CL—closed-loop, OL50 and OL70—open loop stimulation with amplitude 50% and 70% of threshold intensity, respectively, AW—-active wakefulness, PW—passive wakefulness, REM—rapid eye movement sleep, SS—slow wave sleep.
* $p < 0.05$ compared to baseline.

step). Subthreshold stimulation did not cause any motor response.

In order to find out the long-term effects of TMN stimulation we stimulated the rats in a closed-loop mode during 3 h and compared the number and duration of SWDs with those in the 3-hours baseline session. The mean duration of SWDs was 6.9 ± 1.1 s in baseline and 2.1 ± 0.2 s in CL stimulation session. Though each SWD became significantly shorter as a result of stimulation, the overall number of discharges during 3-hours stimulation session increased (84 ± 39 in baseline and 259 ± 165 in CL stimulation session) (Fig. 2). The total duration of epileptic activity displayed no changes (data not shown).

Open-loop TMN stimulation can decrease the number of SWDs

To compare the effects of different stimulation modes on epileptic activity in WAG/Rij rats we also performed open-loop stimulation. Two current intensities were used for each rat—50% and 70% of threshold intensity. OL50 stimulation did not change measured parameters of SWDs. OL70 stimulation also had no influence on the mean duration of SWDs but significantly decreased their number by 40.4 ± 9.2% (Fig. 2). We did not observe abnormal behavior during OL stimulation.

TMN stimulation produces changes in sleep—wake cycle

As the TMN is implicated in the control of wake states, we proposed that electrical stimulation of this nucleus could alter sleep—wake cycle. The total duration of any sleep—wake stage was not changed significantly (Table 1), but we observed that CL stimulation led to fragmentation of animals' activity having increased the number of episodes of AW and PW as well as the total number of episodes (Table 2).

OL50 stimulation did not cause any change in rats' sleep—wake cycle. OL70 stimulation produced motor activation of animals: we observed a marked increase in the number of episodes and total duration of AW accompanied by the reduction of the SS total duration. The total number of episodes was raised as well (Tables 1 and 2).

Table 2 Changes in the number of episodes of different sleep—wake stages during TMN stimulation in a closed-loop and open-loop modes ($n = 5$).

	Baseline	CL	OL50	OL70
AW	193 ± 16	↑* 118 ± 44%	—	↑* 148 ± 78%
PW	256 ± 15	↑* 86 ± 31%	—	—
REM	5 ± 1	—	—	—
SS	69 ± 12	—	—	—
Total	522 ± 29	↑* 84 ± 31%	—	↑* 96 ± 50%

CL—closed-loop, OL50 and OL70—open loop stimulation with amplitude 50% and 70% of threshold intensity, respectively, AW—-active wakefulness, PW—passive wakefulness, REM—rapid eye movement sleep, SS—slow wave sleep.
* $p < 0.05$ compared to baseline.

Discussion

This study showed that high frequency closed-loop stimulation of the TMN was able to interrupt ongoing seizures in a genetic model of absence epilepsy but increased seizure occurrence. Such stimulation induced fragmentation of sleep—wake cycle. We also found that open-loop TMN stimulation with relatively high intensity (70% of threshold) decreased SWD number but led to behavioral activation of the animal and lack of sleep.

SWDs in WAG/Rij rats are generated within a cortico-thalamo-cortical circuit (Inoue et al., 1993; van Luijtelaar and Sitnikova, 2006; Meeren et al., 2002). This circuit includes reciprocal connections between neocortex and relay thalamic nuclei which form the anatomical basis for oscillations (Steriade et al., 1985), and the reticular thalamic nucleus, playing a crucial role in producing synchronization between them (Buzsaki et al., 1988; Steriade et al., 1993). Activation of some structures, due to their anatomical connections and neurochemical properties, may interfere with the epileptic circuit and break synchronous oscillations in it. First of all, these structures may be those responsible for generation and maintenance of sleep—wake states, which are characterized by desynchronized EEG, namely wakefulness and REM-sleep (Jones, 2005; Nishida et al., 2007; Velasco et al., 1997). The TMN is one of the key structures involved in wakeful state regulation (Lin, 2000; Steininger et al., 1999; Rosenwasser, 2009). It sends histaminergic efferents to almost all brain regions and thus is able to induce arousal through both direct projections to the cortex and indirect pathways involving other parts of the arousal system (Brown et al., 2001; Panula et al., 1989, 1990). A number of studies confirm the cortex-activating role of histamine and the TMN (Lin et al., 1988; Monti, 1993; Tasaka et al., 1989; Reiner and Kamondi, 1994). Nishida et al. (2007) have shown that TMN electrical stimulation with frequency 100 Hz causes histamine release in the cortex and desynchronization on EEG. In our study stimulation with the same frequency interrupted ongoing spike-wave epileptic activity generated by cortico-thalamo-cortical network. The mean threshold amplitude of stimulation (78 μA) corresponds with those used for DBS of other targets in genetic absence epilepsy rat models: superior colliculus (76 μA), subthalamic nucleus (100 μA),

anterior thalamic nucleus (114 μA), ventral posteromedial nucleus (72 μA), (Nail-Boucherie et al., 2002; Vercueil et al., 1998; Lüttjohann and van Luijtelaar, 2013). Lower intensity (33 μA) was needed in the case of substantia nigra (Feddersen et al., 2007). This result shows that it is possible to disrupt SWDs by DBS with similar efficiency using a variety of targets.

Most stimulation targets listed above are not parts of the oscillating network and so their antiepileptic action could not be due to direct breaking of the circuit. More likely is that stimulation of these structures influences different elements of the circuit through their efferents and disrupt synchronization. Particularly, the TMN sends its fibers to both cortex and thalamus though the density of histaminergic fibers in the cortex is higher (Panula et al., 1990). It has also indirect connection to these structures through basal forebrain. Therefore it may influence both cortical and thalamic part of the SWD-generating network and both of these pathways may contribute to seizure termination. In CL mode the delay of the stimulation is about 1—2 s, and at this time the SWD is spread over the entire neocortex and to the thalamic nuclei (Meeren et al., 2002; van Luijtelaar and Sitnikova, 2006). Therefore SWD interruption may represent a summarized effect of simultaneous impacts at different points of the network.

During 3-hours CL stimulation period an increase in the amount of discharges occurred. This is consistent with some other studies where a long-term effect of CL stimulation was assessed. Indeed, electric stimulation of thalamus led to an insignificant elevation of SWD amount (Lüttjohann and van Luijtelaar, 2013). Feddersen et al. (2007) observed an increase in SWD number when stimulating the reticular part of substantia nigra in GAERS rats—another genetic absence epilepsy rat model (Danober et al., 1998; Marescaux et al., 1992). Interestingly, Wu et al. (2008) have also observed aggravation of seizure activity by high-frequency TMN stimulation in a kindling model of epilepsy.

SWDs tend to occur during specific periods of sleep—wake cycle, notably passive wakefulness, light slow wave sleep and transition states between wakefulness and sleep (Drinkenburg et al., 1991; Coenen et al., 1991). In these periods the cortico-thalamo-cortical network is believed to be in a certain state which makes it prone to produce synchronous discharges (Coenen et al., 1991; Coenen and van Luijtelaar, 2003; van Luijtelaar and Sitnikova, 2006). Changing activity of the TMN by its electrical stimulation may increase the duration of these preferential states, taking into account the wake-promoting action of the TMN activation and brain histamine elevation (Monti et al., 1986; Nishida et al., 2007; Steininger et al., 1999). Interestingly, we found no augmentation in the total duration of PW, but observed an increase in the number of episodes of both AW and PW, probably associated with stimulation-induced arousals. Such arousals may cause splitting of sleep—wake cycle to shorter periods and appearance of more transitions between vigilance states than in baseline. And this probably leads to aggravation of SWDs.

Open-loop mode of DBS in epilepsy has some disadvantages, i.e. a higher risk of nervous tissue damage and adverse effects as a result of constant stimulation. However, it is easier to perform, because one do not need to analyze EEG to find seizure onset, and can induce long-term plasticity which is regarded as one of the possible therapeutic mechanisms of DBS (Fisher et al., 2010; Lujan et al., 2008; Tye et al., 2009). During OL50 stimulation there were no changes of any measured parameters. Probably the intensity was not enough to produce any alterations. However, using higher stimulation intensity (OL70) induced significant behavioral activation, based on the elevation of the AW amount. Electrical stimulation is unspecific, that is it influences not only particular TMN cells but all cells and fibers at the stimulated area, and can produce either depolarization or hyperpolarization depending on the relative location of the neural element to the electrode tip (Lujan et al., 2008; McIntyre et al., 2004). However, our results suggest that histamine may play a major role in the effect of TMN stimulation, as they are consistent with the data that increased brain histamine concentration lead to intensification of locomotor activity (Sakai et al., 1992; Samotaeva et al., 2012). The decrease in SWD amount during OL70 stimulation is likely to be a secondary effect to the overall behavioral activation as AW is characterized by low probability of SWD occurrence (Drinkenburg et al., 1991).

In conclusion, our study showed that closed-loop TMN stimulation produced contradictory effect on epileptic discharges in a genetic rat model of absence epilepsy. On

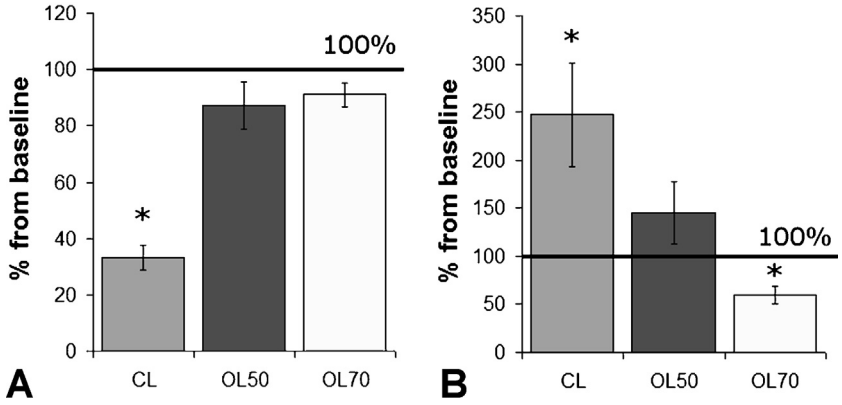

Fig. 2 The effect of 3-hours closed-loop and open-loop stimulation of the TMN on the mean duration (A) and number (B) of SWDs ($n = 5$). * $p < 0.05$ compared to baseline.

the one hand, it successfully interrupted ongoing seizures, on the other it increased seizure occurrence and led to fragmentation of the sleep—wake cycle. Open-loop TMN stimulation was associated with the decrease of SWDs but also induced alterations in the sleep—wake cycle leading to behavioral activation of animals. These data suggest that certain problems may exist when the TMN is used as a target for DBS in epilepsy. However, a broad investigation of stimulation parameters could possibly reveal those producing fewer side effects. This indicates how important it is to choose an appropriate stimulation paradigm and target in DBS for achieving optimal therapeutic outcome. A careful control of sleep—wake activity is necessary because its alteration may lead to seizure aggravation.

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